

REMARKS

Claims 1-38 and 40-50 are pending and under examination in this application. Applicants have reviewed all grounds of rejection issued in the Office Action mailed December 12, 2006, and respectfully traverse for the reasons that follow.

Claims 1-16, 22-27, 31-38, 40-42, 44-47 and 50 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Rothberg et al., U.S. Patent No. 6,274,320, and Walt et al., U.S. Patent No. 6,327,410. The Examiner sets forth three categories of remarks to Applicants' previous Response. Applicants will address each of the Examiner's categories in turn below.

Regarding the Lack of Motivation to Combine:

The Examiner summarily characterizes Applicant's response to the alleged lack of motivation by quoting Applicants concluding statement. The Examiner's reply simply copies verbatim the text of the original rejection, noting that this argument is of record.

Applicants respectfully point out that arguments have been presented supporting Applicants contention that the Office has failed to articulate a *prima facie* case of obviousness. The mere reiteration of two paragraphs quoted from Walt et al. fails to address Applicants original argument and fails to further prosecution on the merits.

Applicants pointed out in their response filed April 14, 2006, that "simply a description of a claimed element does not provide the proper motivation for its combination with a description in another reference absent some teaching, suggestion or motivation to do so. . . . *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004)." *Id.* at paragraph bridging pages 10-11.

Applicants further articulated in their Pre-Appeal Brief Request for Review, filed June 27, 2006, in response to the apparent conclusory statement that the question regarding motivation necessarily should include the method of nucleic acid sequencing of Rothberg et al. Absent inclusion of this element, the Office has failed to establish a *prima facie* case of obviousness because there is no showing of a motivation to combine the cited references to arrive at method containing all claimed elements. In particular, Applicants stated:

However, the question is not whether motivation exists to use beads on a fiber optic surface. Walt et al. describes such a use. Rather, the question is whether:

[O]ne of ordinary skill in the art at the time of the invention [would have been motivated to use] the microspheres of Walt et al. distributed over the surface of the fiber optic sensor in the method of nucleic acid sequencing of Rothberg et al.

Office Action mailed Nov. 28, 2005, at p.10 (emphasis added).

As the rejection stands, the Office has failed to articulate a *prima facie* case of obviousness because the motivation, teaching or suggestion has been completely omitted. The “mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole.” *In re Kahn*, Case No. 04-1616, slip op. at 11 (Fed. Cir. March 22, 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355, 1357 (Fed. Cir. 1998)). As articulated, the mere mention of using beads on a fiber optic surface fails to provide the proper motivation to combine because it does nothing more than identify one element of the claim. (Advisory Action mailed May 1, 2006, at p.2).

Submission filed September 18, 2006, page 10, third paragraph through page 11, second paragraph (emphasis original).

Applicants maintain that any description of using beads in an array fails to provide the proper motivation for using beads in an array for the nucleic acid sequencing method described by Rothberg et al. Further, should the Examiner maintain this ground of rejection, Applicants respectfully request that the Examiner provide a reason why the requisite motivation should not include the nucleic acid sequencing element as is claimed by the invention. The mere quotation of the original rejection fails to satisfy this burden because it is deficient as to the alleged motivation to combine the use of beads in the pyrophosphate sequencing method of Rothberg et al.

Regarding Rothberg et al. Teaching Away:

Applicants have previously substantiated that Rothberg et al. teaches away from the claimed invention. Rothberg et al. explicitly point to reported problems associated with the use of pyrophosphate sequencing in combination with a solid support such as beads (see, for example, Applicant’s Response filed December 19, 2005, at page 11, para. 2; Pre-Appeal Brief Request for Review filed June 27, 2006, at page 2, para. 3 through page 3, para. 3, and

discussion further below). The Office's contention that Walt et al. supplies the element of beads for use in a pyrosequencing method does not overcome this teaching away because one skilled in the art would not have been motivated to combine beads with the Rothberg et al. method of pyrosequencing because of the express teaching away from such use in Rothberg et al. due to bead and sample loss limitations.

The Examiner relies on the allegation that the studies cited by Rothberg et al. were performed with beads suspended in solution to allegedly refute the teaching away that bead loss was a limiting factor. The Examiner has failed to accord patentable weight to Applicants showing that of the various descriptions Rothberg et al. propose to overcome the shortcoming of this limiting factor, none suggest reverting to a bead-based sequencing assay. The fifth proposal apparently relied on by the Examiner describes placing the sequencing reaction in cavities. This proposal addresses prevention of diffusion but there is no recognition by Rothberg et al. that this proposal would address bead loss.

The Examiner also alleges that Applicants have not pointed to other descriptions in Rothberg et al. which support the teaching away that combining pyrophosphate sequencing with microspheres was undesirable. Applicants respectfully disagree and draw the Examiner's attention to the Response filed December 19, 2005, and to Applicants further submitted evidence herewith. In the Response filed December 19, 2005, Applicants specifically pointed to the descriptions in Rothberg et al. to optimizing pyrophosphate sequencing; to considerations of molecular and thermodynamic factors involved in pyrophosphate sequencing, and to reaction configurations that minimize diffusion of pyrophosphate between different templates in light of the previous drawbacks. *Id.* at paragraph bridging pages 11-12. Applicants also addressed the later hypothesis described by Rothberg et al., including the fifth proposal directed to performing reactions in cavities, in the Response filed April 14, 2006. *Id.* at page 12, second paragraph through page 14, first paragraph. In particular, Applicant pointed to the description in Rothberg et al. that characterizes problems associated with bead loss and substantiated this teaching away by showing that all five of the alternative proposals described by Rothberg et al. for performing pyrophosphate sequencing do not suggest reverting to a bead-based method. Such descriptions are sufficient to substantiate that Rothberg et al. teaches away from the claimed invention.

In addition to the express language in Rothberg et al. that Applicants have consistently pointed to, Rothberg et al. explicitly state and advocate for the purposes of an allowance in a continuation-in-part (CIP) application that bead loss was a significant problem in pyrophosphate sequencing methods. The Rothberg et al. CIP application, U.S. Serial No. 09/814,338, is attached hereto as Exhibit A and claims priority to the cited Rothberg et al. '320 patent.

The '320 Rothberg et al. patent was filed September 16, 1999. The only mention of beads employed in pyrosequencing methods is the language Applicants show teaches away from the claimed invention because it teaches that bead loss was a limitation to this method. This teaching away can be found in the '320 Rothberg et al. patent at column 21, lines 14-34 (see, for example, Applicant's Response filed December 19, 2005, at page 11, para. 2). No other mention of beads can be found elsewhere in the document. Therefore, at the time the subject invention was made, Rothberg et al. taught away from beads in pyrosequencing methods and Applicants explicitly claim such use.

Rothberg et al.'s CIP application, later filed on March 21, 2001, more than one year after the subject application's actual filing date, expressly incorporates the use of beads in pyrosequencing methods and relies heavily on this element as being critical to the inventiveness of the CIP claims in order to achieve an allowance. For example, a stated consideration by the Office in issuing a Notice of Allowance for the CIP application was Rothberg's continued assertions and submitted declarations that bead and sample loss limit the sequencing methods. In the Examiner Reasons for Allowance, the Examiner stated:

The diameter range, the depth, and well-depth of the claimed caviated fiber optic wafer . . . are deemed non-obvious over the general teaching provided for by Chee et al. (of record), based on Margulies Declaration, as each of the above-mentioned parameters are critical to the laminar flow of the reaction reagents . . . (see page 3 bottom paragraph to page 4, top paragraph; Margulies Declaration).

Notice of Allowability mailed February 7, 2007, at page 2 (emphasis added). Attached as Exhibit B.

The statements and evidence relied on by the Office include: (1) characterization of the application to contain an express acknowledgement that bead loss was a limitation in pyrosequencing methods; (2) Rothberg's express confirmation during prosecution that bead loss

limited pyrosequencing methods and that the application expressly recognizes this problem; (3) statements by a declarant attesting that bead loss was a limitation in pyrosequencing methods and that the application expressly recognizes this limitation, and (4) statements by a declarant attesting that the well depth in array-based pyrosequencing methods is not arbitrary.

In particular, Rothberg et al. expressly recognizes bead loss to be a limitation in pyrosequencing methods in the CIP application. The recognized language corresponds to Applicants' cited teaching away in the '320 patent and states:

However, it was found that the loss of the beads during washing, which was performed between each nucleotide and enzyme addition, limited the technique to short sequences.

Exhibit A, at page 39, lines 22-24 (emphasis added); *see also*, the '320 Rothberg et al. patent at column 21, lines 30-34 and Applicant's Response filed December 19, 2005, at page 11, para. 2.

This teaching away is confirmed during prosecution of the CIP application when Rothberg's Response states:

[T]he application expressly recognizes the problem of bead/sample loss during the sequencing reaction (see, *inter alia*, page 37, lines 6-9, page 39, lines 22-24; and Figure 4).

Response filed April 23, 2004, attached as Exhibit C, at page 20, para. 2 (emphasis added).

Therefore, both the Rothberg '320 patent and the Rothberg et al. CIP application contain an express recognition that bead loss was a limiting factor in pyrosequencing methods. Rothberg himself expressly confirms this teaching away during prosecution of the CIP application.

During prosecution of the CIP application, statements made in a declaration filed in support of the Response arguments, attached as Exhibit D, also confirm the above acknowledgements. In particular, Dr. Margulies attests:

The application expressly recognizes the problem of bead/sample loss during the sequencing reaction. This teaching is found, *inter alia*, in the originally filed application on p. 37, l. 6-9, p. 39, l. 22-24; and Fig. 4). . . . Accordingly, the claimed apparatus and substrate yield significantly improved results, which are not obtained with other sequencing systems . . .

Exhibit D, Margulies Declaration executed April 20, 2004, at para. 17-18 (emphasis added).

In a second declaration, Dr. Margulies also attests:

[T]he claimed parameters for well diameter . . . and well depth . . . are not arbitrarily chosen parameters. Well depth is selected on the basis of a number of competing requirements in a nucleic acid sequencing application: (1) wells need to be deep enough for DNA-carrying beads to remain in the wells . . .

Exhibit E, Margulies Declaration executed December 22, 2006, at para. 8.

Therefore, on two different occasions during prosecution of the CIP application Dr. Margulies, who is skilled in the art, attests that the application expressly recognizes bead loss to be a problem in previous pyrosequencing methods and that well depth is an important parameter when using beads in pyrosequencing methods.

The newly included of express language to the use of beads in pyrosequencing methods in the Rothberg CIP application and advocacy that this discovery overcomes the problems associated with such previous methods shows that Rothberg et al. previously taught away from the use of beads, but later changed his mind. In particular, the new matter added to the Rothberg et al. CIP can be found at, for example, paragraphs [0120] and [0127]-[0137] and exemplary state:

In various embodiments, some components of the reaction are immobilized, while other components are provided in solution. For example, in some embodiments, the enzymes utilized in the pyrophosphate sequencing reaction (e.g., sulfurylase, luciferase) may be immobilized if desired onto the solid support. Similarly, one or more of the enzymes utilized in the pyrophosphate sequencing reaction, e.g., sulfurylase, luciferase may be immobilized at the termini of a fiber optic reactor array. Other components of the reaction, e.g., a polymerase (such as Klenow fragment), nucleic acid template, and nucleotides can be added by flowing, spraying, or rolling. In still further embodiments one more of the reagents used in the sequencing reactions is delivered on beads.

Exhibit A, at page 31, lines 21-29 (emphasis added).

Rothberg's inclusion of the above express teachings evidence that he was in possession of the use of beads only after the filing date of the '320 Rothberg et al. patent. The Rothberg et al. CIP prosecution further shows:

- the parent application failed to mention the use of beads in a pyrosequencing method other than its teaching away that bead loss is limiting in pyrosequencing methods;
- confirms through descriptions in both the '320 patent and through statements made by Applicants' representative and by declarant testimony that the Rothberg applications expressly recognize bead loss to be a limiting problem;
- the CIP application expressly incorporated the use of beads in pyrosequence methods, showing that Rothberg et al. was not in possession of this element, indicated to be critical, until after the subject application, and
- the Office relied on these statements and supporting documents to issue a Notice of Allowance of the CIP application.

Such evidence strongly corroborates Applicants' showing that the Rothberg et al. '320 patent teaches away from the use of beads in a pyrosequencing method because the '320 patent contains only negative teachings whereas the CIP application contains express language showing Rothberg et al. was in possession of the use of beads only after the filing of the earlier '320 patent. Hence, Rothberg's change of direction and express admission that previous use of beads was problematic in order to achieve allowance shows that Rothberg only later discovered what Applicant of the instant application has maintained throughout the record. Namely, that the use of beads in pyrosequencing methods was unobvious over the art at least because the art taught away from this embodiment.

Regarding the Problem Facing the Inventors:

The Office alleges that the application lacks any indication that Applicant attempted to solve the problem of PPI diffusion and that also appears to testify that the described array densities are "far too close to distinguish PPI signals originating from different beads." Office Action at page 6, second paragraph.

Applicants respectfully point out that with respect to the apparent lack of an indication that the problem facing the inventor was PPI diffusion, there is no statutory or judicial precedent requiring Applicant to set forth such a requirement. *In re Kahn*, Case No. 04-1616, slip op. at 15 (Fed. Cir., March 22, 2006) articulates that the inventors problem is the proper view from which

to address the motivation-suggestion-teaching requirement of § 103(a). Therefore, the assertion that there is no indication in the application appears to be an inappropriate response to applicants Response.

Further, and in contrast to the Examiner's assertion, the application describes that pyrophosphate sequencing using a substrate comprising microspheres is one preferred embodiment. In particular, the application teaches:

Accordingly, a preferred embodiment of the methods of the invention is as follows. A substrate comprising microspheres containing the target sequences and extension primers, forming hybridization complexes, is dipped or contacted with a volume (reaction chamber or well) comprising a single type of dNTP, an extension enzyme, and the reagents and enzymes necessary to detect PPi.

Id. at page 10, lines 13-16 (emphasis added).

Accordingly, in light of this description, Applicants have made clear that one preferred embodiment of the invention over previous methods is the use of a pyrophosphate sequencing in combination with a substrate having microspheres.

Finally, with respect to the Office's assertion that the described array densities are "far too close to distinguish PPi signals originating from different beads," Applicants' respectfully point out that such a statement appears to be apparent testimony or conclusory because it is unsubstantiated. If the Examiner insists on maintaining this rationale based on her personal expertise or other evidence, Applicants respectfully request such expertise or other evidence to be substantiated and made of record. Applicants will respond to any such proffered facts once they are made of record.

In light of the above remarks, Applicants maintain that the claims are unobvious over the cited combination of Rothberg et al. and Walt et al. Therefore, withdrawal of this ground of rejection is respectfully requested.

Regarding the Kit Claims:

With respect to the kit claims of claims 18, 19, 28-30 and 43, under 35 U.S.C. § 103(a) as allegedly obvious over Rothberg et al., Walt et al., Nyren et al. and the Stratagene Catalog,

Applicants respectfully draw the Examiner's attention to the arguments of record. In particular, Applicants have pointed out that the Office has maintained this ground of rejection based on its apparent rebuttal of Applicants' arguments over Rothberg et al. However, as pointed out, Rothberg et al. teaches away from combining pyrophosphate sequencing with microspheres and that none of the citations in either the primary or secondary reference teach, suggest provide the proper motivation to combine pyrophosphate sequencing with a solid support such as a microsphere (see, for example, Response filed April 14, 2006, page 15, second paragraph through page 16, first paragraph). Absent such a teaching, suggestion or motivation, the invention as claimed is not rendered obvious over the cited references. Applicants maintain and reassert this argument of record. Specifically, absent a *prima facie* showing of motivation to combine the cited references to arrive at all claimed elements of the base claims, the further combination of references to additional elements fails to cure the deficiencies for a *prima facie* showing. Accordingly, this ground of is respectfully requested to be withdrawn.

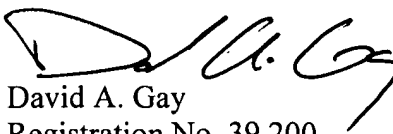
CONCLUSION

In light of the above Remarks, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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